UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,772	11/13/2007	Aiping H. Young	50120/008001	4680

21559 7590 11/05/2009

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SHIN, DANA H	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/585,772	YOUNG ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-34 and 52-55* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 22-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-14-09; 10-19-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on September 2, 2009.

Currently, claims 1-20, 22-34, 52-55 are pending. Claims 1-17 and 52-55 have been withdrawn from further consideration as being drawn to a non-elected invention. Accordingly, claims 18-20 and 22-34 are under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on October 14, 2009 is being considered by the examiner except the GenBank and Press Release citations, whose legible copies are not submitted.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Priority

The benefit of the 60/535,496 filing date remains denied for claims 18-20, 22-30 and 32-34 as failing to provide adequate written description for the claimed subject matter under 35 U.S.C., first paragraph for the reasons of record as set forth in the Office action mailed on April 2, 2009 and for the reasons stated below.

Applicant's arguments filed on September 2, 2009 have been fully considered but they are not persuasive. Applicant argues that the disclosure of 60/535,496 provides adequate support for the claimed method step of administering "one or more immunotherapeutic agents", wherein the agents are "non-specific immunotherapeutic agents", "specific immunotherapeutic agents", "cytokine", "non-cytokine adjuvant", "monoclonal antibody", "cancer vaccine". In arguing so, applicant points out pages 15-16 of the provisional application. It is noted that page 15 (see lines 9-11 as pointed out by applicant) provides a disclosure that combination treatment comprising an antisense oligonucleotide and "one or more chemotherapeutic agents", wherein the chemotherapeutic agents (not immunotherapeutic agents) include "cytokines". It is noted that page 16 (see lines 3-5 and 9-10 as pointed out by applicant) teaches a combination therapy comprising the antisense oligonucleotide and one or more "cytokines" or a "cytokine". Applicant therefore asserts that the combination therapy comprising the antisense oligonucleotide and cytokines (subclass of the genus of immunotherapeutic agents) provides adequate support for the entire genus of immunotherapeutic agents, further in view of the "extensive teaching" provided in 60/535,496 at pages 23-30 and working Examples. It is found that there is nothing whatsoever in the passages pointed out by applicant that adequately describes the entire genus of the term "immunotherapeutic agents", let alone the specifically claimed agents in the instant case. Note

that the claimed "immunotherapeutic agents" are in no way limited to "cytokines" disclosed as chemotherapeutic agents in 60/535,496 as evidenced by dependent claims (e.g., claims 27-30) and as evidenced by the applicant-provided definition for the term "immunotherapeutic agent" such that includes but is not limited to cytokines, cancer vaccines, monoclonal antibodies and non-cytokine adjuvant. See page 9. Hence, at best, the disclosure of 60/535,496 provides written description for the method step of administering one or more cytokines; however, it fails to provide adequate support for the claimed method encompassing the entire genus of immunotherapeutic agents as well as the specifically enumerated species in the manner provided by the first paragraph of 35 U.S.C. 112. Hence, the benefit of an earlier filing date for claims 18-20, 22-30 and 32-34 is granted only insofar as the filing date of 60/602,817, which is August 18, 2004.

Claim Rejections - 35 USC § 102

Claims 18-20, 23, 25, 28-29, and 33-34 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wright et al. for the reasons of record as set forth in the Office action mailed on June 22, 2009 and for the reasons stated below.

Applicant's arguments filed on September 22, 2009 have been fully considered but they are not persuasive. Applicant argues that Wright et al. do not teach a combination of antisense oligonucleotide against ribonucleotide reductase R2 and an immunotherapeutic agent, which shows "an improved efficacy of the use of the antisense oligonucleotides alone." In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "improved efficacy") are not recited in

the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, contrary to applicant's argument that Wright et al. do not teach the combination therapeutic methods claimed in the instant case, Wright et al. explicitly state the following at page 15: "For therapeutic applications, the oligonucleotides, ribozymes, antisense oligonucleotides, antibodies, and substances and compounds identified using the methods of the invention may be formulated into pharmaceutical compositions. The pharmaceutical compositions may ***comprise one or more*** oligonucleotides, ribozymes, ***antisense oligonucleotides, antibodies***, and substances and compounds identified using the methods of the invention for administration to subjects in a biologically compatible form suitable for administration to a subject.", wherein the reduction of ribonucleotide reductase R2 treats proliferative disorders such as cancer. (emphasis added). Hence, Wright et al. teach all claim limitations and therefore anticipate the claims. Accordingly, this rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 18-20 and 22-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. and Pavlick et al. for the reasons of record as set forth in the Office action 3mailed on April 2, 2009 and for the reasons stated below.

Applicant's arguments filed on September 2, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims are not obvious over the cited prior art references because there is no significant difference between groups treated with chemotherapy alone and groups treated with both chemotherapy and IL-1 and IFN as taught by Pavlick et al.

Applicant's attention is directed to the fact that there is no requirement in the claims as currently written that the combination of antisense oligonucleotide and a cytokine must result in a "better" treatment effect compared to single agent-therapy. Further, the fact that combination therapeutic strategies for treating cancer (e.g., combination of an antisense oligonucleotide and a chemotherapeutic agent; combination of chemotherapy and immunotherapy) were known in the art as taught by Wright et al. and Pavlick et al.

Applicant asserts that "the success of such biochemotherapies was still uncertain." Note that for obviousness under §103, "all that is required is a reasonable expectation of success", and it does not require "absolute predictability of success". See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681. Further, contrary to applicant's assertion, Pavlick et al. taught that one of ordinary skill in the art was sufficiently equipped with techniques to devise a non-toxic biochemotherapeutic strategy by sequentially administering chemotherapeutic agent followed by IL-2 and/or IFN "in order to limit the combined toxicities of the drugs." See page 1553. Moreover, Pavlick et al. also taught improved or superior therapeutic effects of combination therapy compared to single agent-based monotherapy as they state the following: "the results of a large, randomized Phase III trial of CVD plus IL-2 plus IFN given sequentially compared to CVD alone. The trial showed that biochemotherapy was ***superior*** to chemotherapy" (emphasis added). See page 1553. See also the various biochemotherapy clinical trials listed in Table 3. Hence, examiner dose not understand applicant's allegation that the success of biochemotherapy was uncertain at the time the invention was made. Further, cytokines (e.g., IL-12, IFN), antibodies, and antisense oligonucleotides were all known to be anti-cancer therapeutic agents. See Table 2 of Pavlick et al. Taken together, there was a reasonable expectation of

success for one of ordinary skill in the art to devise a combination therapeutic strategy for treating cancer comprising administering three different anti-cancer therapeutic agents: 1) an antisense oligonucleotide targeted to SEQ ID NO:42 of Wright et al.; 2) one or more chemotherapeutic agents such as CVD of Pavlick et al.; and 3) one or more immunotherapeutic agents such as cytokines and antibodies.

Applicant argues that the claims are not obvious because Pavlick et al. alone or in combination with Wright et al. do not teach combination of an antisense oligonucleotide with a cytokine. Contrary to applicant's argument, an antisense oligonucleotide (see G3139 of Genasense listed in Table 2) was a known anti-cancer therapeutic agent that can be effectively used in combination with chemotherapeutic agents as G3139 in combination with decarbazine was under the phase III clinical trial (see page 1555) at the time the invention was made. Further, the instantly claimed antisense oligonucleotide targeted against SEQ ID NO:1 was an art-recognized anti-cancer agent that can be used in combination with a chemotherapeutic agent as taught by Wright et al. Since the anti-cancer therapeutic efficacy of chemotherapeutic agents was known to be improved when combined with a cytokine as taught by Pavlick et al., it would have been obvious to one of ordinary skill in the art to further add a cytokine to the dual combination therapy comprising an antisense oligonucleotide and a chemotherapeutic agent. Note that claim 32 specifically requires all three agents and claim 18 does not exclude a chemotherapeutic agent as the method recites the open-ended, inclusive transitional phrase "comprising". See MPEP 2111.03.

Applicant argues that the claims are not obvious because the specification shows "improved inhibition of cancer growth" for the claimed combination methods compared to single

agent. Contrary to applicant's argument, the improved therapeutic effects for cancer treatment via a combination therapy compared to monotherapy were sufficiently suggested in the art as taught by Pavlick et al. (see page 1553). As such, the asserted "improved" cancer growth inhibition is not unexpected. Further, the passages pointed out by applicant (Examples 2-7 and Figures 2-7) do not show the asserted unexpected results that are commensurate in scope with the claims as they show a combination of the antisense oligonucleotide with a very specific species of immunotherapeutic agent (IL-2 or IFN alpha) and with a very specific species of chemotherapeutic agent (mitomycin C or CPT-11 or 5-FU).

Since applicant's arguments do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited, this rejection is maintained.

New Rejections Necessitated by IDS Submission

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-20 and 22-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheult et al. (*Abstracts of the General Meeting of the American Society for Microbiology,* 2002, applicant's citation), Auer et al. (*43rd Annual Meeting of the American Society of Hematology,* 2001, applicant's citation), Abaza et al. (*Annual Meeting of the Federation of American Societies for Experimental Biology,* 2001, applicant's citation) in view of Wright et al. (WO 00/47733, applicant's citation).

Scheult et al. teach that an antisense oligonucleotide targeted to TGF-beta in combination with IL-12 synergistically enhances the anti-tumor effect of the antisense oligonucleotide. See the entire reference.

Auer et al. teach that an antisense oligonucleotide targeted to Bcl-2 (G3139 of Genasense) in combination with rituximab or dexamethoasone or fludarabine confers enhanced anti-tumor activity and that the antisense oligonucleotide synergistic with the immunotherapeutic agent. See the entire reference.

Abaza et al. teach that one can improve cancer treatment effects by combining an antisense oligonucleotide targeted to C-myb with either a standard cytotoxic (chemotherapeutic) agent or an immunotherapeutic agent such as IFN gamma and IFN beta. See the entire reference.

None of Scheult et al., Auer et al., Abaza et al. teach using an antisense oligonucleotide targeted to ribonucleotide reductase R2.

Wright et al. teach that an antisense compound "AS-II-626-20" that has the nucleotide sequence of "GGCTAAATCGCTCCACCAAG", which is identical to the claimed sequence of SEQ ID NO:1 effectively inhibits tumor cell proliferation *in vivo* in mice. Furthermore, they show that the "AS-II-626-20" compound is more effective in reducing tumor volume/weight than antisense compounds targeted to Bcl-2 or C-myb. See Tables 1, 13-14; Figure 23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer "AS-II-626-20" compound in combination with any of art-recognized anti-cancer, immunotherapeutic agent, further in combination with a chemotherapeutic agent.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because combination therapeutics comprising different classes of anti-

cancer agents, especially antisense oligonucleotides in combination with immunotherapeutic agents or chemotherapeutic agents were known to confer synergistic cancer treatment effects as taught by Scheult et al., Auer et al., and Abaza et al. Since the "AS-II-626-20" compound was known to be more effective in reducing tumor weight/volume in mice than the anti-Bcl-2 antisense oligonucleotide of Auer et al., or the anti-C-myb antisense oligonucleotide of Abaza et al., one of ordinary skill in the art would have been motivated to replace the anti-Bcl-2 or anti-C-myb antisense oligonucleotide with "AS-II-626-20" compound of Wright et al. in the combination cancer therapy methods of Auer et al. and Abaza et al. Since all skills and knowledge required to arrive at the claimed invention were known in the art at the time the invention was made, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This application contains claims 1-17 and 52-55 drawn to inventions nonelected with traverse in the reply filed on March 4, 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on October 14, 2009 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. ANGELL/
Primary Examiner, Art Unit 1635